REMARKS

A. Regarding the Amendments

Claims 1, 5, 6, 11, 17 and 20 have been amended as set forth in the attached "Version With Markings To Show Changes Made." As amended, the claims are supported by the specification and the original claims. Thus, upon entry of the amendments, claims 1-22 will be pending.

B. Attorney Docket Number

Please note that the attorney docket number for this application should be PROV1100-2, not PROV1100-1. A request for corrected filing receipt accompanies this response, requesting the same correction.

C. Objection Under 37 C.F.R. 1.172(a)

The present application was objected to under 37 C.F.R. 1.172(a) as the assignee allegedly has not established its ownership interest in the U.S. Patent No. 6,037,366. Applicants respectfully draw the Examiner's attention to the documents submitted herewith. Included in these documents are:

- Exhibit A: a statement under 37 C.F.R. 3.73(b) signed by Gary Loomis, Vice President of Research and Development for Provasis Therapeutics, Inc.;
- Exhibit B: a copy of the assignment executed by inventors Robert E. Krall, Charles W. Kerber and Kimberly Knox, assigning U.S. Application Serial No. 09/151,621 to Prohold Technologies, Inc., as submitted to the U.S. Patent and Trademark Office (USPTO) on December 23, 1998;
- Exhibit C: a copy of the assignments recorded on December 28, 1998 in the USPTO at Reel 9666; Frame 0731 for U.S. Application Serial No. 09/151,621; and

- Exhibit D: copies of the documents showing the name change of Prohold Technologies, Inc. to Provasis Therapeutics, Inc.

As such, it is respectfully submitted that the ownership rights of the assignee, Provasis Therapeutics, Inc., are herein established.

D. Objection Under 37 C.F.R. 1.173

The Examiner has objected to the application as allegedly missing columns 1 and 2 of the patent. Applicants respectfully disagree. At one place in the reissue application, the marked up copy is provided which only contains the cover sheet and columns 3 and 4 of the patent. However, the ribbon copy of the patent was also provided, which continued the cover page and columns 1 to 4. Accordingly the full text of the patent on double column form was provided with the filing of the application. However, in the interest of ensuring that all requirements have been complied with, Applicants are enclosing herein a complete, unmarked copy of the issued patent with each page on one side of the paper as Exhibit E. Removal of this objection is therefore respectfully requested.

Additionally, the present application is objected to as not complying with the requirements of MPEP 1411 regarding the mark up of column 4. As MPEP 1411 cites 37 C.F.R. 1.173 as stating that amendments may be made by either markup of the patent or by preliminary amendment, please disregard the marked-up copy of the patent and enter the amendments to the claims as requested in the preliminary amendments filed March 30, 2001 and November 12, 2001. It is unclear if the Examiner objects further to the form of the application. Clarification of the objection is respectfully requested if the preceding text does not adequately address the Examiner's objections.

Applicants acknowledge the Examiner's note that the preliminary amendment filed March 30, 2001 and the marked up copy of the patent contain the same amendments. It is respectfully submitted that the preliminary amendment should not contain the "Twice Amended"

designation, as the amendments indicated in both places are the same amendment. The claims have only been amended once, though the changes are shown in two places in the submission.

E. Rejection Under 35 U.S.C. 251

The claims of the invention are also rejected as being based upon new matter added to the patent. Applicants respectfully disagree.

Independent claims 1, 5, 6, 11, 17 and 20 are rejected as allegedly containing new matter with regard to the term "fatty acid ester." As indicated above, such fatty acid esters have been limited to fatty acid esters in liquid form. This language is supported in the patent at, for example, col. 2, lines 1-3 and col. 3, lines 47-50.

Claims 6 and 11 are rejected as possessing a cyanoacrylate in part 1 and a stabilized polymer of cyanoacrylate in part 2. As set forth above, the independent claims have been clarified, such that it is clear that the cyanoacrylates of parts 1 and 2 are the same. Accordingly, removal of the rejection is respectfully requested.

Claims 6, 11, 17 and 20 are rejected as containing new matter in the term "radiopaque metal powder." Applicants respectfully disagree with the allegation that the disclosure fails to convey use of radiopaque metal powders other than gold. It is Applicants position that the application provides support for tantalum, platinum and gold.

As previously set forth, support for claims 6, 11, 17 and 20 is found in the specification of the patent at, for example, column 3, lines 42-45. This section states, in part that tantalum, platinum and gold are all radiopaque and may therefore be used in the present invention for the radiopaque metal powder. Gold is set forth as the best mode.

It is stated in Paper No. 5 that the specification fails to convey that all other radiopaque metals would be suitable alternatives. Applicants respectfully disagree. In support of Applicants' position that the specification would have enabled use of a claimed composition,

containing radiopaque materials other than gold, an article by Spiegel et al. is submitted herewith as Exhibit F. (Spiegel, S. M. et al., "Adjusting the Polymerization Time of Isobutyl-2 Cyanoacrylate," *American Journal of Neuroradiology*, Vol. 7, Jan/Feb 1986, pgs. 109-112.) In the Materials and Methods section of that reference, Spiegel et al. describe use of tantalum, another type of radiopaque material, in a composition for embolization of an artery or its branches. Tantalum in that reference is shown to not react with the other constituents of the mixture and by its presence makes the mixture more viscous and more radiopaque. (Spiegel, et al., p. 110.) As such, it is submitted that Spiegel et al. confirm that one skilled in the art would have been able to make and use a composition of the invention using radiopaque materials other than gold, such as tantalum, for embolization at the time of filing of the present application.

CONCLUSION

In summary, for the reasons set forth herein, Applicants maintain that claims 1-22 clearly and patentably define the invention, respectfully request that the Examiner reconsider the various grounds set forth in the Office Action, and respectfully request the allowance of the claims which are now pending.

If the Examiner would like to discuss any of the issues raised in the Office Action, Applicant's representative can be reached at (858) 677-1456. Please charge any additional fees, or make any credits, to Deposit Account No. 50-1355.

Respectfully submitted,

Date: October 1, 2002

Lisa A. Haile, J.D., Ph.D.
Registration No. 38,347
Telephone: (858) 677-1456
Facsimile: (858) 677-1465

GRAY CARY WARE & FREIDENRICH LLP
4365 Executive Drive, Suite 1100
San Diego, California 92121-2133
USPTO Customer Number 28213

VERSION WITH MARKINGS TO SHOW CHANGES MADE

1. (Twice Amended) A composition for creating therapeutic vascular occlusions in an animal comprising a mixture of:

(a) Part 1 comprised of 2-hexyl cyanoacrylate, hydroquinone, p-methoxyphenol and phosphoric acid; and

(b) Part 2 comprising gold metal powder, a fatty acid ester in liquid form and a stabilized polymer of 2-hexyl cyanoacrylate.

5. (Twice Amended) A method for creating therapeutic vascular occlusions in an animal needing therapeutic vascular occlusion comprising the steps of:

(a) Mixing together Part 1 comprised of 2-hexyl cyanoacrylate, hydroquinone, p-methoxyphenol and phosphoric acid with Part 2 comprising gold metal powder, a fatty acid ester in liquid form, and a stabilized polymer of 2-hexyl cyanoacrylate; and

(b) administering the mixture into a vascular site needing occlusion.

6. (Once Amended) A composition for creating therapeutic vascular occlusions in an animal comprising a mixture of:

(a) Part 1 comprised of a cyanoacrylate liquid monomer, hydroquinone, p-methoxyphenol and phosphoric acid; and

(b) Part 2 comprising a radiopaque metal powder, a fatty acid ester in liquid form and a stabilized polymer of cyanoacrylate, wherein the cyanoacrylate is the same as the cyanoacrylate of part 1.

11. (Once Amended) A method for creating therapeutic vascular occlusions in an animal needing therapeutic vascular occlusion comprising the steps of:

(a) mixing together Part 1 comprised of cyanoacrylate, hydroquinone, p-methoxyphenol and phosphoric acid with Part 2 comprising a radiopaque metal powder, a fatty acid ester in liquid form and a stabilized polymer of cyanoacrylate, wherein the cyanoacrylate is the same as the cyanoacrylate of part 1; and

(b) administering the mixture into a vascular site needing occlusion.

17. (Once Amended) A composition for creating therapeutic vascular occlusions in an animal comprising a mixture of:

(a) Part 1 comprised of 2-hexyl cyanoacrylate, hydroquinone, p-methoxyphenol and phosphoric acid, wherein the p-methoxyphenol is 1200 ppm; and

(b) Part 2 comprising a radiopaque metal powder, a fatty acid ester in liquid form and a stabilized polymer of 2-hexyl cyanoacrylate.

20. (Once Amended) A composition for creating therapeutic vascular occlusions in an animal comprising a mixture of:

(a) Part 1 comprised of 2-hexyl cyanoacrylate, hydroquinone, p-methoxyphenol and phosphoric acid, wherein the p-methoxyphenol is from 100 ppm to 1200 ppm; and

(b) Part 2 comprising a radiopaque metal powder, a fatty acid ester in liquid form and a stabilized polymer of 2-hexyl cyanoacrylate.

PTO/SB/53 (02-01)
Approved for use through 01/31/2004. OMB 0651-0033
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

REISSUE APPLICATION: CONSENT OF ASSIGNEE; STATEMENT OF NON-ASSIGNMENT

Docket Number (Optional)
PROV1100-1

This is part of the application for a reissue patent based on the original patent identified below.

Name of Patentee(s) Robert E. Krall, Charles W. Kerber, and Kimberly Knox

Patent Number 6,037,366

Date Patent Issued March 14, 2000

Title of Invention COMPOSITION FOR CREATING VASCULAR OCCLUSIONS

1. [X] Filed herein is a statement under 37 CFR 3.73(b). (Form PTO/SB/96)

2. [ ] Ownership of the patent is in the inventor(s), and no assignment of the patent is in effect.

One of boxes 1 or 2 above must be checked. If multiple assignees, complete this form for each assignee. If box 2 is checked, skip the next entry and go directly to "Name of Assignee".

The written consent of all assignees and inventors owning an undivided interest in the original patent is included in this application for reissue.

The assignee(s) owning an undivided interest in said original patent is/are PROHOLD MEDICAL TECHNOLOGIES, INC. and the assignee(s) consents to the accompanying application for reissue.

Name of assignee/inventor (if not assigned)

Signature

Date 3/30/01

Typed or printed name and title of person signing for assignee (if assigned)

Gary L. Loomis
Vice President, Research & Development

PTO/SB/96 (08-00)
Approved for use through 10/31/2002. OMB 0651-0031
U.S.Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

STATEMENT UNDER 37 CFR 3.73(b)

Applicant/Patent Owner: Robert E. Krall, Charles W. Kerber, and Kimberly Knox

Application No./Patent No.: 6,037,366 Filed/Issue Date: March 14, 2000

Entitled: COMPOSITION FOR CREATING VASCULAR OCCLUSIONS

PROVASIS THERAPEUTICS, INC., a Delaware corporation,

(Name of Assignee) (Type of Assignee, e.g., corporation, partnership, university, government agency, etc.)

states that it is:

1. [X] the assignee of the entire right, title, and interest; or

2. [ ] an assignee of less than the entire right, title and interest.
The extent (by, percentage) of its ownership interest is _____%

in the patent application/patent identified above by virtue of either:

A. [X] An assignment from the inventor(s) of the patent application/patent identified above. The assignment was recorded in the United States Patent and Trademark Office at Reel _____, Frame _____, or for which a copy thereof is attached.

OR

B. [ ] A chain of title from the inventor(s), of the patent application/patent identified above, to the current assignee as shown below:

1. From:_____ To:_____
The document was recorded in the United States Patent and Trademark Office at Reel _____, Frame_____, or for which a copy thereof is attached.

2. From:_____ To:_____
The document was recorded in the United States Patent and Trademark Office at Reel _____, Frame_____, or for which a copy thereof is attached.

3. From:_____ To:_____
The document was recorded in the United States Patent and Trademark Office at Reel _____, Frame_____, or for which a copy thereof is attached.

[ ] Additional documents in the chain of title are listed on a supplemental sheet.

[X] Copies of assignments or other documents in the chain of title are attached.
[NOTE: A separate copy *(i.e.,* the original assignment document or a true copy of the original document) must be submitted to Assignment Division in accordance with 37 CFR Part 3, if the assignment is to be recorded in the records of the USPTO. See MPEP 302.08]

The undersigned (whose title is supplied below) is authorized to act on behalf of the assignee.

March 30, 2001
Date

Gary L. Loomis
Typed or printed name

Signature

Vice President, Research & Development
Title

UTILITY/DESIGN PATENT
Docket N . P52.2-7161

ASSIGNMENT

WHEREAS, we, Robert E. Krall; Charlet W. Kerber; Kimberly Knox residing at 2728 Via Dieguenos, Alpine, California 91901; 4444 Tapa Tapa Drive, LaMesa, California 91941-7160, ; 4444 Tapa Tapa Drive, LaMesa, California 91941-7160 have invented and own the entire United States right, title and interest in an invention for:

COMPOSITION FOR CREATING VASCULAR OCCLUSIONS

disclosed in our application for United States Letter Patent filed:

on September 11, 1998 and assigned Serial No. 09/151,621; and

I hereby authorize and request any attorney of Vidas, Arrett & Steinkraus, P.A., Suite 2000, 6109 Blue Circle Drive, Minnetonka, MN 55343-9131, to insert the filing date and application number of said application above when known.

WHEREAS, Prokoid Technologies, Inc. ("Assignee"), a corporation organized and existing under and by virtue of the laws of the State of California, and having its principal place of business at 1444 Pioneer Way, Suite 12, El Cajon, California 92020, is desirous of acquiring the entire right, title, and interest in and to said invention, to said application for any and all countries, to any and all Letters Patent, and to any and all Design Letters Patent of any and all countries which may be granted thereon;

NOW, THEREFORE, Be It Known that for good and valuable consideration, the receipt of all of which is hereby acknowledged, I(we) hereby sell, assign, and transfer unto Assignee, its successors, and assigns, the entire right, title and interest, legal and equitable, in and to said invention, to said application for any and all countries, to any and all Letters Patent, and to any and all Design Letters Patent of any and all countries which may be granted thereon; and the Commissioner of Patents and Trademarks is hereby authorized and requested to issue all Letters Patent and all Design Letters Patent which may be granted to said invention to Assignee.

Dated: _____ First Inventor's Signature: _____
First Inventor's Name: Robert E. Krall

Dated: _____ Second Inventor's Signature: _____
Second Inventor's Name: Charles W. Kerber

Dated: _____ Third Inventor's Signature: _____
Third Inventor's Name: Kimberly Knox

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Application of:	Charles W. KERBER et al.
Application No.:	09/151,621
Filed:	September 11, 1998
For:	COMPOSITION FOR CREATING VASCULAR OCCLUSIONS
Examiner:	*(Not yet assigned)*
Group Art Unit:	1711

Box Assignment
Assistant Commissioner for Patents
Washington, D.C. 20231

Docket No.: P52.2-7161

TRANSMITTAL LETTER

1. In regard to the above-identified application, we are submitting the attached:
1 pg. Recordation Form Cover Sheet; 1 pg. Assignment; Check for $40.00; VA&S Transmittal Letter; and Postcard.

2. With respect to fees:
   - ☐ No additional fee is required.
   - ☒ Attached is check(s) in the amount of $ 40.00 .
   - ☐ Charge additional fee to our Deposit Account No. 22-0350.

CONDITIONAL PETITION AND FEE FOR EXTENSION OF TIME

3. This conditional petition is being filed along with the papers identified in Item 1 above and provides for the possibility that Applicant has inadvertently overlooked the need for a petition and fee for extension of time. If any extension of time for the accompanying response is required, Applicant requests that this be considered a petition therefor.

4. Please charge any additional fees or credit overpayment associated with this communication to Deposit Account No. 22-0350.

VIDAS, ARRETT & STEINKRAUS

Date: December 23, 1998

By: _____
Richard A. Arrett
Registration No. 33,153

6109 Blue Circle Drive, Suite 2000
Minnetonka, MN 55343-9131
Telephone: (612) 563-3000
Facsimile: (612) 563-3001

Certificate Under 37 CFR 1.8: I hereby certify that this Transmittal Letter and the paper(s) as described herein, are being deposited in the U.S. Postal Service, as FIRST CLASS MAIL, addressed to Box Assignment, Assistant Commissioner for Patents, Washington D.C. 20231, on December 23, 1998.

Julie A. Parle
Julie A. Parle

Form PTO-1595
1-31-92

U.S. DEPARTMENT OF COMMERCE
Patent and Trademark Office

RECORDATION FORM COVER SHEET
PATENTS ONLY

To the Honorable Commissioner of Patents and Trademarks. Please record the attached original documents or copy thereof.

1. Name of conveying party(ies):
Robert E. Krall; Charles W. Kerber; Kimberly Knox

Additional name(s) of conveying party(ies) attached? ☐ Yes ☒ No

2. Name and address of receiving party(ies):
Name: **Prohold Technologies, Inc.**

Internal Address:

Street Address: **1444 Pioneer Way, Suite 12**

City: **El Cajon** State: **California** Zip: **92020**

Additional name(s) & address(es) attached? ☐ Yes ☒ No

3. Nature of Conveyance:
☒ Assignment ☐ Merger
☐ Security Agreement ☐ Change of Name
☐ Other _____
Execution Date: 12/23/98

4. Application number(s) or patent number(s):
If this document is being filed with a new application, the execution date of the application is:

A. Patent Application No.(s)
09/151,621

B. Patent No.(s)

Additional numbers attached? ☐ Yes ☒ No

5. Name and address of party to whom correspondence concerning document should be mailed:

Scott Q. Vidas
Vidas, Arrett & Steinkraus, P.A.
Suite 2000, 6109 Blue Circle Drive
Minnetonka, MN 55343-9131

6. Total number of applications and patents involved: ___1___

7. Total fee (37 CFR 3.41): $40.00
☒ Enclosed
☐ Authorized to be charged to deposit account

8. Deposit Account Number: **22-0350**
(Attach duplicate of this page if paying by deposit account)

DO NOT USE THIS SPACE

9. Statement and signature.

To the best of my knowledge and belief, the foregoing information is true and correct and any attached copy is a true copy of the original document.

Richard A. Arrett, Esq.

Signature

12/23/98
Date

Total number of pages including cover sheet, attachments, and document: 2

OMB No. 0651-011 (exp. 4/94)

Do not detach this portion

Mail documents to be recorded with required cover sheet information to:
Commissioner of Patents and Trademarks
Box Assignments
Washingt n, D.C. 20231

VIDAS, ARRETT & ST[redacted]AUS
PATENT, TRADEMARK & COPY[redacted]CAUSES
SUITE 2000
6109 BLUE CIRCLE DRIVE
MINNETONKA, MN 55343-9131 • (612) 563-3000

REMITTANCE ADVICE					
		[redacted]			

17-1/910

15393

PAY Forty dollars and NO/100 DOLLAR

TIME WK'D	DATE	TO THE ORDER OF				NET AMOUNT
	12/23/98	Asst. Comm. of Patents	ARF: P52.2-7161			40

VIDAS, ARRETT & STEINKRAUS

NORWEST BANK MINNESOTA, N.A.
NORWEST CENTER OFFICE
8th ST. & MARQUETTE AVE. MINNEAPOLIS, MN

AMOUNTS EXCEEDING $1,000 REQUIRE TWO SIGNATURES

FOR SECURITY PURPOSES, THIS DOCUMENT CONTAINS MICROPRINTING IN THE BORDER AND AN ARTIFICIAL WATERMARK ON THE REVERSE SIDE. HOLD AT AN ANGLE TO VIEW.

⑈015393⑈ ⑆091000019⑆ 003150⑈

THIS WILL ACKNOWLEDGE RECEIPT OF THE FOLLOWING IN THE U.S. PAT AND TM OFFICE. ENCLOSURES: VA&S Transmittal Letter 1 pg. Recordation Form Cover Sheet; 1 pg. Assignment; Check for $40.00

APPLICANT: Charles W. KERBER et al.

SERIAL NO. 09/151,621 DOCKET NO: P52.2-7161

PRIORITY DATE:

CLIENT: Prohold Technologies, Inc.

MAILED: By First Class Mail on December 23, 199

RAA:jap

THIS WILL ACKNOWLEDGE RECEIPT OF THE FOLLOWING IN THE U.S. PAT AND TM OFFICE. ENCLOSURES: VA&S Transmittal Letter; 1 pg. Recordation Form Cover Sheet; 1 pg. Assignment; Check for $40.00

APPLICANT: Charles W. KERBER et al.

SERIAL NO. 09/151,621 DOCKET NO: P52.2-7161

PRIORITY DATE:

CLIENT: Prohold Technologies, Inc.

MAILED: By First Class Mail on December 23, 1998

RAA:jap

610-79277

Patent Assignment Abstract of Title

NOTE: Searching may be done for issued patents only. Please consult USPTO staff members for access to patent assignment data related to pending and/or abandoned applications.

Total Assignments: 1

Patent No: 6037366 **Issue Dt:** 03/14/2000 **Appl. No:** 09151621 **Filing Dt:** 09/11/1998

Title: COMPOSITION FOR CREATING VASCULAR OCCLUSIONS

Assignment: 1

Reel/Frame: 009666/0730 **Date Recorded:** 12/28/1998 **Number of Pages:** 2

Conveyance: ASSIGNMENT OF ASSIGNORS INTEREST (SEE DOCUMENT FOR DETAILS).

Assignor: KRALL, ROBERT E. **Exec Dt:** 12/23/1998
KERBER, CHARLES W. **Exec Dt:** 12/23/1998
KNOX, KIMBERLY **Exec Dt:** 12/23/1998

Assignee: PROHOLD TECHNOLOGIES, INC.
1444 PIONEER WAY, SUITE 12
EL CAJON, CALIFORNIA 92020

Correspondent: VIDAS, ARRETT & STEINKRAUS, P.A.
SCOTT Q. VIDAS
SUITE 2000
6109 BLUE CIRCLE DRIVE
MINNETONKA, MN 55343-9131

Results as of: 8/29/2002 1:35:44 P.M.

If you have any comments or questions concerning the data displayed, contact OPR / Assignments at 703-308-9723

Date Last Updated: 01/31/2002

01-04-1999

Form PTO-1595
1-31-92

U.S. DEPARTMENT OF COMMERCE
Patent and Trademark Office

REC 100934953

PATENTS ONLY

MRD 12.28.98

To the Honorable Commissioner of Patents and Trademarks. Please record the attached original documents or copy thereof.

1. Name of conveying party(ies):
Robert E. Krall; Charles W. Kerber; Kimberly Knox

Additional name(s) of conveying party(ies) attached? ☐ Yes ☒ No

2. Name and address of receiving party(ies):
Name: **Prohold Technologies, Inc.**

Internal Address:

Street Address: **1444 Pioneer Way, Suite 12**

City: **El Cajon** State: **California** Zip: **92020**

Additional name(s) & address(es) attached? ☐ Yes ☒ No

3. Nature of Conveyance:
☒ Assignment ☐ Merger
☐ Security Agreement ☐ Change of Name
☐ Other _____
Execution Date: 12/23/98

4. Application number(s) or patent number(s):
If this document is being filed with a new application, the execution date of the application is:

A. Patent Application No.(s)
09/151,621

B. Patent No.(s)

Additional numbers attached? ☐ Yes ☒ No

5. Name and address of party to whom correspondence concerning document should be mailed

Scott Q. Vidas
Vidas, Arrett & Steinkraus, P.A.
Suite 2000, 6109 Blue Circle Drive
Minnetonka, MN 55343-9131

6. Total number of applications and patents involved: 1

7. Total fee (37 CFR 3.41): $40.00 E
☒ Enclosed
☐ Authorized to be charged to deposit account

8. Deposit Account Number: **22-0350**
(Attach duplicate of this page if paying by deposit account)

DO NOT USE THIS SPACE

9. Statement and signature.

To the best of my knowledge and belief, the foregoing information is true and correct and any attached copy is a true copy of the original document.

Richard A. Arrett, Esq.

Signature

12/23/98
Date

Total number of pages including cover sheet, attachments, and document: 2

OMB No. 0651-011 (exp. 4/94)

Do not detach this portion

Mail documents to be recorded with required cover sheet information to:
Commissioner of Patents and Trademarks
Box Assignments
Washington, D.C. 20231

12/30/1998 JWATKINS 00000098 09151621
01 FC:581 40.00

[redacted] [redacted]

UTILITY/DE[redacted]N PATENT
Docket N . P52.2-7161

ASSIGNMENT

WHEREAS, we, Robert E. Krall; Charles W. Kerber; Kimberly Knox residing at 2728 Via Dieguenos, Alpine, California 91901; 4444 Tapa Tapa Drive, LaMesa, California 91941-7160, ; 4444 Tapa Tapa Drive, LaMesa, California 91941-7160 have invented and own the entire United States right, title and interest in an invention for:

COMPOSITION FOR CREATING VASCULAR OCCLUSIONS

disclosed in our application for United States Letter Patent filed:

on September 11, 1998 and assigned Serial No. 09/151,621; and

I hereby authorize and request any attorney of Vidas, Arrett & Steinkraus, P.A., Suite 2000, 6109 Blue Circle Drive, Minnetonka, MN 55343-9131, to insert the filing date and application number of said application above when known.

WHEREAS, Prohold Technologies, Inc. ("Assignee"), a corporation organized and existing under and by virtue of the laws of the State of California, and having its principal place of business at 1444 Pioneer Way, Suite 12, El Cajon, California 92020, is desirous of acquiring the entire right, title, and interest in and to said invention, to said application for any and all countries, to any and all Letters Patent, and to any and all Design Letters Patent of any and all countries which may be granted thereon;

NOW, THEREFORE, Be It Known that: for good and valuable consideration, the receipt of all of which is hereby acknowledged, I(we) hereby sell, assign, and transfer unto Assignee, its successors, and assigns, the entire right, title and interest, legal and equitable, in and to said invention, to said application for any and all countries, to any and all Letters Patent, and to any and all Design Letters Patent of any and all countries which may be granted thereon; and the Commissioner of Patents and Trademarks is hereby authorized and requested to issue all Letters Patent and all Design Letters Patent which may be granted to said invention to Assignee.

Dated: _____ First Inventor's Signature: _____
First Inventor's Name: Robert E. Krall

Dated: _____ Second Inventor's Signature: _____
Second Inventor's Name: Charles W. Kerber

Dated: _____ Third Inventor's Signature: _____
Third Inventor's Name: Kimberly Knox

0556734

State of California

OFFICE OF THE SECRETARY OF STATE

SECRETARY OF STATE

I, *BILL JONES*, Secretary of State of the State of California, hereby certify:

That the attached transcript of 1 page(s) has been compared with the record on file in this office, of which it purports to be a copy, and that it is full, true and correct.

IN WITNESS WHEREOF, I execute this certificate and affix the Great Seal of the State of California this day of

DEC 15 2000

Bill Jones

Secretary of State

Sec/State Form CE-107 (rev. 8/98)

OSP 98 13524

A055[redacted]4

DO NOT WRITE IN THIS SPACE

AMENDED STATEMENT BY FOREIGN CORPORATION

ENDORSED - FILED
in the office of the Secretary of State
of the State of California

DEC 0 7 2000

BILL JONES, Secretary of State

Provasis Therapeutics Inc., a corporation

organized and existing under the laws of Delaware and which is presently qualified for the transaction of intrastate business in the State of California, makes the following statement:

That the name of the corporation has been changed to that hereinabove set forth and that the name relinquished at the same time of such change was Prohold Medical Corporation

Provasis Therapeutics Inc.
(Name of Corporation)

(Signature of Corporate Officer)

John W. Cardosa, Chief Financial Officer
(Typed Name and Title of Officer Signing)

OFFICE OF THE SECRETARY OF STATE

Gray Cary\GT\6212817.1
105458-159923

State of Delaware
Office of the Secretary of State

I, EDWARD J. FREEL, SECRETARY OF STATE OF THE STATE OF DELAWARE, DO HEREBY CERTIFY THE ATTACHED IS A TRUE AND CORRECT COPY OF THE CERTIFICATE OF AMENDMENT OF "PROHOLD MEDICAL CORPORATION", CHANGING ITS NAME FROM "PROHOLD MEDICAL CORPORATION" TO "PROVASIS THERAPEUTICS INC.", FILED IN THIS OFFICE ON THE SEVENTEENTH DAY OF NOVEMBER, A.D. 2000, AT 9 O'CLOCK A.M.

A FILED COPY OF THIS CERTIFICATE HAS BEEN FORWARDED TO THE KENT COUNTY RECORDER OF DEEDS.

Edward J. Freel, Secretary of State

3114023 8100

001581026

AUTHENTICATION: 0804286

DATE: 11-20-00

STATE OF DELAWARE
SECRETARY OF STATE
DIVISION OF CORPORATIONS
FILED 09:00 AM 11/17/2000
001581026 - 3114023

CERTIFICATE OF AMENDMENT OF RESTATED CERTIFICATE OF INCORPORATION OF PROHOLD MEDICAL CORPORATION.

Prohold Medical Corporation, a corporation organized and existing under and by virtue of the General Corporation Law of the State of Delaware, does hereby certify:

FIRST: That at a meeting of the Board of Directors, resolutions were duly adopted setting forth a proposed amendment to the Certificate of Incorporation of said corporation, declaring said amendment to be advisable and calling for a written consent of the stockholders of said corporation for consideration thereof. Pursuant to such resolutions, Article First of the Corporation's Certificate of Incorporation is amended and restated in its entirety as follows:

"1.

The name of the corporation is Provasis Therapeutics Inc. (the "Corporation" or the "Company")."

SECOND: That thereafter, pursuant to resolution of its Board of Directors, a written consent of the stockholders of said corporation was duly solicited and executed, pursuant to which the necessary number of shares as required by statute and by said corporation's Certificate of Incorporation, as amended, were voted in favor of the amendment.

THIRD: That said amendment was duly adopted in accordance with the provisions of Section 242 of the General Corporation Law of the State of Delaware.

IN WITNESS WHEREOF, said corporation has caused this certificate to be signed and attested by its duly authorized officer this 7th day of November, 2000.

By: _____
John W. Cardosa, Secretary

State of Delaware

Office of the Secretary of State

I, EDWARD J. FREEL, SECRETARY OF STATE OF THE STATE OF DELAWARE, DO HEREBY CERTIFY THE ATTACHED IS A TRUE AND CORRECT COPY OF THE CERTIFICATE OF AMENDMENT OF "PROHOLD MEDICAL CORPORATION", FILED IN THIS OFFICE ON THE FOURTEENTH DAY OF JUNE, A.D. 2000, AT 9 O'CLOCK A.M.

A FILED COPY OF THIS CERTIFICATE HAS BEEN FORWARDED TO THE KENT COUNTY RECORDER OF DEEDS.

Edward J. Freel, Secretary of State

3114023 8100

001302884

AUTHENTICATION: 0498049

DATE: 06-15-00

RECEIVED TIME MAR.29. 9:03AM

[redacted]037366A

United States Patent [19]

Krall et al.

[11] Patent Number: 6,037,366

[45] Date of Patent: Mar. 14, 2000

[54] COMPOSITION FOR CREATING VASCULAR OCCLUSIONS

[75] Inventors: Robert E. Krall, Alpine; Charles W. Kerber; Kimberly Knox, both of LaMesa, all of Calif.

[73] Assignee: Prohold Medical Technologies, Inc., El Cajon, Calif.

[21] Appl. No.: 09/151,621

[22] Filed: Sep. 11, 1998

Related U.S. Application Data

[60] Provisional application No. 60/058,510, Sep. 11, 1997.

[51] Int. Cl.[7] A61K 31/275; A61K 31/12; A61K 31/05; A61K 33/24

[52] U.S. Cl. 514/527; 514/526; 514/690; 514/730; 514/558; 514/560; 514/824; 514/834; 514/930; 514/944; 514/970; 424/601; 424/605; 424/649; 424/78.08; 424/78.31; 424/78.37; 604/49; 604/53

[58] Field of Search 514/526, 527, 514/690, 730, 558, 560, 824, 834, 930, 944, 970; 424/601, 605, 649, 78.08, 78.31, 78.37; 604/49, 53

[56] References Cited

U.S. PATENT DOCUMENTS

4,740,534	4/1988	Matsuda et al.	523/111
5,525,334	6/1996	Ito et al.	424/78.35
5,624,685	4/1997	Takahashi et al.	424/488
5,695,480	12/1997	Evans et al.	604/264
5,702,361	12/1997	Evans et al.	604/53
5,759,194	6/1998	Hammerslag	606/214

Primary Examiner—John Pak
Attorney, Agent, or Firm—Campbell & Flores LLP

[57] ABSTRACT

A composition including 2-hexyl cyanoacrylate and gold is useful in treating arteriovenous malformations (AVMs) and other body lumens to be blocked.

5 Claims, No Drawings

COMPOSITION FOR CREATING VASCULAR OCCLUSIONS

This application claims the benefit of U.S. Provisional Application No. 60/058,510, filed on Sep. 11, 1997.

BACKGROUND OF THE INVENTION

1. Field of the Invention

This invention relates to a composition used to treat arteriovenous malformations ("AVMs") and other vascular abnormalities. The composition includes a cyanoacrylate liquid monomer and gold in a prepolymerized polymer of cyanoacrylate. The composition is placed into the body lumen via standard catheter procedures or directly percutaneously.

2. Description of the Related Art

AVMs and vascular tumors, especially those of the brain, are exceedingly difficult to treat. These growths may occur all over the body, but are especially difficult to treat when in the brain or brain stem. The composition of the invention is especially useful in treating neurological AVMs, but may also be used to treat tumors anywhere in the body.

Cyanoacrylate adhesives have been used surgically but are limited in their usefulness by cytotoxicity and heat generation. The brain is unusually sensitive to cytotoxicity and heat.

The art described in this section is not intended to constitute an admission that any patent, publication or other information referred to herein is "prior art" with respect to this invention, unless specifically designated as such. In addition, this section should not be construed to mean that a search has been made or that no other pertinent information as defined in 37 C.F.R. § 1.56(a) exists.

SUMMARY OF THE INVENTION

The invention provides a composition that may be placed in a body lumen including veins and arteries by super selective catheterization or direct puncture using standard tools of the interventional angiographer. The composition of the invention has been successfully tested in simulated models of the AVMs and tumors under fluoroscopy and in systems that closely resembles the neurological condition of the human body. Further studies have been done in the pig rete. The rete is a body of fine arteries that allows the blood to flow into the pig brain which closely resembles normal human AVMs.

The composition is a cyanoacrylate which involves mixing two separate containers of the material immediately prior to administration of the material into the AVM by catheter. The composition may contain seven ingredients which are divided into two parts prior to mixture and use. It furnishes properties that are useful for closing neurological AVMs. The product can also be used to close any growth resembling an AVM in any part of the body. Because of the sensitive nature of the tissues in the brain, the general sensitivity of the product must be controlled. In less sensitive areas, the product will work equally as well.

Part I consists of a cyanoacrylate liquid monomer containing pure phosphoric acid (250 ppm) hydroquinone (100 ppm) and P-methoxyphenol (1200 ppm). This composition is stable and unchanging we believe for over two years. The container in which Part I is stored requires cleaning and preparation before such stability can be achieved. The liquid monomer of choice for this usage is 2-hexyl cyanoacrylate.

Part II consists of pure powdered gold (5±3 microns), a small amount of prepolymerized polymer of the same cyanoacrylate and ethyl myristate. Any of the large chain fatty acid esters will work to replace ethyl myristate so long as they are liquids.

The pre-polymerized polymers of cyanoacrylate are unstable and change their structures and properties even in the solid state. The change is exponential and therefore the polymer must be used within a limited amount of time before deterioration occurs.

The polymer is prepared by addition of part 1 to a rapidly stirring weak bicarbonate-water solution. The addition must be added drop-wise to avoid unpolymerized masses from forming. The solid polymer is washed thoroughly with pure water to remove any traces of bicarbonate, then washed thoroughly with pure methanol to remove the water. Methanol dries rapidly and when the polymer is further dried at a high reduced pressure for 16–18 hours, it is considered dry. The polymer must be used in the next step within 24 hours to obtain consistent results in the final product. This mixture must be sterilized within 72 hours from the time of preparation.

Part II is sterilized with ethylene oxide gas with the stopper held in an open position. Ethylene oxide is an alkylating agent and after sterilization the prepolymerized polymer is stable. Hence, the stability and sterilization of part 2 are carried out simultaneously. The sterilized samples of Part II are capped in a clean room under sterile handling conditions.

The pre-polymerized polymer can be stabled by treatment with any of the strong alkylating agents, like ethylene oxide, ketene, etc.

This composition of matter has good cohesion as well as adequate adhesion to function well for AVMs and other similar uses within the vascular tree. The cohesion keeps the material together during the time required for it to polymerize. The adhesion makes it stick to the artery walls.

The polymerized device will cause a modest but desirable inflammatory response in the treated tissues.

A Formulation for Arteriovenous Malformations and Tumors

It is desirable to prepare a formulation for the intravascular occlusion of AVMs and Tumors that will have the following properties:

- The product has a very slow rate of biodegradation.
- Both liquid and solid forms should have excellent cohesion.
- The delivered product should have medium adhesion
- The delivered product must be radiopaque.
- The solid polymer should be soft and pliable.
- The delivered product must have a very low or negligible histotoxicity.
- The deposited product must have no long term negative properties such as carcinogenicity, teratogenicity, systemic toxicity or other unpredictable biological and medical effects.
- The products must be sterile.
- The delivered product must have good flow characteristics for selective catheterization.
- The product must be stable on storage for an extended period of time.
- The formulation should be made from pure products and be reproducible for simple manufacturing procedures.

The product formulation is:

Part I (M1)	
2-Hexyl Cyanoacrylate	999,550 ppm
Hydroquinone	100 ppm
p-Methoxyphenol	100 ppm
Pure Phosphoric Acid	250 ppm
Part II (M2)	
Pure Gold	1.0000 g
Pure Ethyl Myristate	0.5000 g
FMS*	0.0200 g

*FMS is a specially prepared polymer of 2-hexyl cyanoacrylate and must be used within 24 hours of preparation or will change and be unusable. Further, it must be sterilized within 72 hours.

Each item of this formulation is critical to the proper performance of the product.

2-Hexyl Cyanoacrylate

This cyanoacrylate homolog was chosen because it biodegrades very slowly in blood or any living tissue. The secondary alcohol will biodegrade several thousand times slower than its primary derivative. This very slow degradation rate also lowers greatly the histotoxicity.

Hydroquinone

When the amount of hydroquinone is reduced by half (50 ppm) the product shows low shelf life stability. Large amounts over 100 ppm do not seem to effect the product stability. This inhibitor lowers the effect of the high energy free radicals that may appear in the cyanoacrylate.

p-Methoxyphenol

The slow polymerization of cyanoacrylates even under refrigeration is caused by low energy free radicals. When 100 ppm of p-methoxyphenol is present this slow polymerization is prevented and long term stability is achieved. Less p-methoxyphenol (50 ppm) will not protect the product.

Sulfur Dioxide

The faintest trace of sulfur dioxide is present in the product. One part per million can be seen and less is present. However, this very faint trace adds to the stability of Neuracryl* ml in the ampule.

Gold

Tantalum, platinum and gold are all radiopaque. Gold was best for us because it could be suspended colloidally in the mixture. One gram of gold is used per device.

Ethyl Myristate

Subbicates, fatty acid esters and other plasticizers, are useful for fastening the polymers of the cyanoacrylates. they also will stabilize the pre-formed polymers of the cyanoacrylates so that they may be used as thickeners. We have chosen ethyl myristate, an esterified, biocompatible fatty acid because of the convenience of purification and analysis and because is works well to give the formulation the desirable properties.

FMS

FMS is the polymer of 2-hexyl cyanoacrylate formed in a weak, aqueous sodium bicarbonate solutions. The polymer differs in structure and size depending on how it is formed. This polymer will remain stable until M2 can be formulated. The polymer must be formed and dried completely before use. The final formulation of M2 must occur within 24 hours because the ethyl myristate stabilized FMS until sterilization can be performed. After sterilization the product is stable for several years.

Neuracryl M

M1 and M2 are mixed immediately before use. The mixture should be used within 4 hours after mixing. If there is a delay, the syringe should be turned over several times a minute to resuspend the gold which will be settled.

What is claimed is:

1. A composition for creating therapeutic vascular occlusions in an animal comprising a mixture of:

(a) Part 1 comprised of 2-hexyl cyanoacrylate, hydroquinone, p-methoxyphenol and phosphoric acid; and

(b) Part 2 comprising gold metal powder, ethyl myristate and a sterilized polymer of 2-hexylcyanoacrylate in weak aqueous bicarbonate solution.

2. The composition of claim 1 wherein Part 1 comprises about 100 PPM hydroquinone, 100 PPM p-methoxyphenol, 250 PPM phosphoric acid and the remainder 2-hexyl cyanoacrylate.

3. The composition of claim 2 wherein Part 2 comprises about 65 percent by weight gold, about 30 percent by weight ethyl myristate and the remainder said sterilized polymer of 2-hexylcyanoacrylate in weak aqueous bicarbonate solution.

4. The composition of claim 1 wherein Part 2 includes sulfur dioxide as a stabilizer.

5. A method for creating therapeutic vascular occlusions in an animal needing therapeutic vascular occlusion comprising the steps of:

(a) Mixing together Part 1 comprised of 2-hexyl cyanoacrylate, hydroquinone, p-methoxyphenol and phosphoric acid with Part 2 comprising gold metal powder, ethyl myristate and a sterilized polymer of 2-hexylcyanoacrylate in weak aqueous bicarbonate solution; and

(b) injecting the mixture into a vascular site needing occlusion with the gold metal powder suspended in the mixture.

* * * * *